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Published in:
Infectious diseases and therapy

DOI:
[10.1007/s40121-018-0221-2](https://doi.org/10.1007/s40121-018-0221-2)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wilson, M. R., Wasserman, M., Jadavji, T., Postma, M., Breton, M-C., Peloquin, F., Earnshaw, S. R., McDade, C., Sings, H. L., & Farkouh, R. (2018). Response to McGirr et al.'s Comment on "Clinical and Economic Impact of a Potential Switch from 13-Valent to 10-Valent Pneumococcal Conjugate Infant Vaccination in Canada". *Infectious diseases and therapy*, 7(4), 539-543. <https://doi.org/10.1007/s40121-018-0221-2>

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LETTER

Response to McGirr et al.'s Comment on "Clinical and Economic Impact of a Potential Switch from 13-Valent to 10-Valent Pneumococcal Conjugate Infant Vaccination in Canada"

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Received: October 16, 2018
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Keywords: Cost-effectiveness; Health economics; Pneumococcal disease; Vaccination

We thank McGirr and colleagues for their interest in our manuscript entitled "Clinical and Economic Impact of a Potential Switch from 13-Valent to 10-Valent Pneumococcal Conjugate Infant Vaccination in Canada." They raise several questions related to our novel approach to pneumococcal disease modeling, and we appreciate the opportunity to provide further clarification.

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1. Differences in serotype distribution as well as immunization rates vary between provinces, and use of regional data may not be representative of the whole of Canada.

In their letter, McGirr et al. question the choice of the data set used for our model input and its representativeness of national trends. They further cite several other data sets with broader national reach as more appropriate for our analysis. In Canada, decisions about, and administration of, immunization programs are made on a provincial level, and programs differ between jurisdictions with respect to the year of introduction, immunization schedules implemented, and vaccine used, etc. (e.g., some provinces had a short period of PCV10 use, while the majority transitioned directly to PCV13).

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Subsequently, any surveillance program that collects data on a national basis (such as IMPACT <https://www.cps.ca/en/impact> and National Microbiology Laboratory (NML) surveillance) represents a mixture of these different provincial immunization programs. In addition, NML surveillance—only available starting in 2011—is passive, and the Public Health Agency of Canada cautions on the interpretation of these data (PHAC, [14]). Surveillance is based on provincial reporting into the NML, which is done on a voluntary basis, and provinces may submit only a subset of laboratory isolates for testing. The CNDSS data set does not include serotyping information, and the eIMD data set is a pilot project launched in 2011 in the small province of New Brunswick; therefore, these were not considered appropriate for our modeling.

Because our modeling approach is based on the historical behavior of each serotype, it was crucial to have access to a serotype-specific data set by age and by year starting from 2001. Data from the Toronto Invasive Bacterial Diseases Network (TIBDN), an active, population-based, long-standing surveillance initiative, satisfied these criteria. While we acknowledge the limitations of extrapolating a single province to the rest of Canada, we believe this selection of data set was a conservative one, as use of data from Quebec—where quality surveillance data are also available—produced more favorable ICERs towards PCV13 and was previously presented at the 2016 Canadian Immunization Conference [19].

2. The approach taken is not recommended by ISPOR or SMDM guidelines.

McGirr and colleagues claim that the ISPOR-SMDM task force guidelines call for state-transition models, discrete event simulations, or dynamic transmission models as the best-practice approach [2]. While the approaches were noted as commonly used methods, it was not presented as an exhaustive list of acceptable methods. As noted in the introduction of our article, while a dynamic transmission model could have been developed to answer the question, data limitations, complexity of the model, and lack of information to support the numerous parameters in such a model would

have limited its relevance. As such, we developed a straightforward, transparent model driven by observed, real-world evidence rather than clinical efficacy. This is a critical differentiator of our approach from various other pneumococcal disease models that rather use clinical efficacy assumptions or methods that do not or differently capture indirect effects [17].

3. Concerns about the trend lines and methodology.

McGirr and colleagues note concerns about the methodology, particularly around the R^2 values. Low R^2 values were primarily observed in serotypes responsible for few or no cases of disease (e.g., serotypes 1 and 6A) or in populations in which incidence was low (ages 18–34, 35–49 years). Therefore, in these cases the impact is expected to be modest as the model predicted few cases to occur for either vaccine. Over 70% of cases were observed in the < 5 and > 65 year populations and driven primarily by serotype 19A where model fits were strong (R^2 values > 0.79). We think that R^2 provided an unbiased approach to the selection of the mathematical function to represent the vaccine, serotype, and age group. While we did not include the trend lines in the probabilistic sensitivity analysis—as we have no mathematical estimates of the uncertainty of the data—we performed sensitivity analyses using various trend lines from countries that have implemented either PCV13 or PCV10 to capture uncertainty in vaccine behavior under different epidemiologic settings. These analyses would likely predict comparable ranges to traditional sensitivity analysis around the base case.

4. Potential cross-reactivity of the 10-valent vaccine with serotype 19A.

McGirr and colleagues correctly allude to a pair of case-control studies in Finland and Brazil that suggested cross-protection of the 10-valent vaccine with serotype 19A [9, 12]; however, their statement that “the approach used by Wilson et al. did not account for this cross-reactivity against serotype 19A” is not correct. The strength of our novel methodology is that explicit assumptions on cross-reactivity, vaccine

efficacy, and related parameters are not necessary; our model incorporates longitudinal vaccine performance under real-world settings. Therefore, the model utilizes data that inherently account for any 19A cross-protection (or any other serotypes for that matter). This 19A evidence has been summarized in depth in a recent systematic review [11]. Furthermore, surveillance data after a switch from PCV13 to PCV10 in Belgium became available after the publication of our manuscript [8]. By the end of 2017, only 8 to 18 months following the switch to PCV10 in the two Belgian regional immunization programs (Flanders in July 2015 and Wallonia in May 2016), a nationwide tenfold increase in serotype 19A IPD cases in children ≤ 2 years of age was observed with this trend continuing into 2018 [8]. However, further analyses of these data are required before definite conclusions can be drawn.

5. Impact on mucosal disease.

McGirr and colleagues challenge the approach of extrapolating serotype-specific IPD incidence to acute otitis media (AOM) and pneumonia. While we agree that predictions of AOM and pneumonia are complicated by the presence of multiple causative pathogens, this method is well accepted as changes in IPD incidence would be driven by changes in circulating carriage of disease-causing serotypes [15–17].

McGirr and colleagues also suggest that the model omits any potential benefit of PCV10 in reducing cases of AOM caused by non-typeable *Haemophilus influenzae* (NTHi) and that this exclusion biases the results against PCV10. Previous cost-effectiveness studies favoring PCV10 are strongly driven by this benefit [3, 7, 10, 18, 20]. However, we believe that additional evidence for both vaccines is necessary to quantify the impact on AOM beyond *S. pneumoniae* (such as NTHi or any other pathogen causing AOM) in cost-effectiveness analyses [1, 5, 6, 13, 17]. Therefore, we took a conservative approach by excluding NTHi impact from our analyses. This was outlined in our manuscript and has been summarized in depth elsewhere [13, 17].

6. Results are inconsistent with the health economic assessment conducted by the

Comité sur l'immunisation du Québec (CIQ).

A recent analysis by CIQ including children < 5 years and only IPD found a 2 + 1 PCV10 schedule would be cost-effective compared with a 2 + 1 PCV13 schedule [4]. We note that our analysis differs in that it includes: the impact of indirect effects (impact in the population ≥ 5 years), impact of PCVs on non-invasive disease (pneumonia and otitis media), and impact of disease on QALYs lost; most importantly, our analysis accounts for the costs required to treat additional cases of disease resulting from a switch to a 2 + 1 PCV10 schedule.

In closing, we thank McGirr and colleagues for their thorough assessment of our article. We acknowledge that our results are prone to specific assumptions, and alternate assumptions could lead to alternate results, although our results were robust to sensitivity analyses performed. We hope that our answers clarified our analysis.

ACKNOWLEDGEMENTS

Funding. This work was sponsored by Pfizer Inc. No article processing charges were received by the journal for the publication of this letter.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Michele Wilson is an employee of RTI Health Solutions, who were paid consultants to Pfizer in connection with the development of this manuscript. Stephanie Earnshaw is an employee of RTI Health Solutions, who were paid consultants to Pfizer in connection with the development of this manuscript. Cheryl McDade is an employee of RTI Health Solutions, who were paid consultants to Pfizer in connection with the development of this manuscript. Maarten Postma was a paid

consultant to Pfizer (or received an honorarium from Pfizer) in connection with the development of this manuscript. Matt Wasserman is an employee of Pfizer Inc. Marie-Claude Breton is an employee of Pfizer Inc. Francois Peloquin is an employee of Pfizer Inc. Heather L. Sings is an employee of Pfizer Inc. Raymond Farkouh is an employee of Pfizer Inc. Taj Jadavji has nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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